

**APPENDIX I**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of	)	
Francesse GIANCARLO <i>et al.</i>	)	Group Art Unit: 1614
Application Serial No.: 10/589,751	)	Examiner: Savitha M. RAO
Filed: August 17, 2006	)	Confirmation No.: 9535
For: A PROCESS FOR THE	)	
PREPARATION OF CRYSTALLINE	)	
(6RS)-N(5)-FORMYL-5,6,7,8-	)	
TETRAHYDROFOLIC ACID	)	

**DECLARATION UNDER 37 CFR.1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Sir:

I, Fabrizio Marazza, declare as follows:

1. The diastereoisomeric purity of (6S)-Folinic Acid and of the (6S)-Sodium Folate or (6S)-Potassium Folate solution derived there from is determined only by the diastereoisomeric purity of the starting material (6S)-Calcium Folate. At the same time the diastereoisomeric purity of (6S)-Calcium Folate is determined only by the diastereoisomeric purity of the precursor (6S)-5,6,7,8-Tetrahydrofolic Acid. The isomeric purity as such does not change during this transformations, i.e., formylation, of (6S)-5,6,7,8-Tetrahydrofolic Acid and salt formation of the obtained (6S)-Folinic Acid.
2. In example 2 of the US Patent Application No. 10/589,751 it is stated that (6S)Calcium Folate is "prepared according to EP 600 460 and NO 172 492". EP 600 460

corresponds to U.S. Patent No. 5,489,684. U.S. Patent No. 5,489,684 discloses in claim 1 that the (6S)-5,6,7,8-Tetrahydrofolic Acid has a diastereoisomeric purity of "at least 75%". In Example 1, at column 4, line 13 of U.S. Patent No. 5,489,684, the diastereoisomeric purity is described as "80.5%". In Example 2, at column 4, line 29 of U.S. Patent No. 5,489,684 the diastereoisomeric purity is described as "93%". Accordingly, the diastereoisomeric purity of the (6S)-Sodium Folate or (6S)-Potassium Folate solution prepared according to EP 600 460 and NO 172 492 will be at least 75%.

3. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code.

F. Marazza  
Fabrizio Marazza, PhD  
IP manager  
Cerbios-Pharma SA  
Barbengo,

August 24, 2010  
Date

Attorney's Docket No.: 705152-2001  
Application No.: 10/589,751

## **APPENDIX II**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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Francesco GIANCARLO <i>et al.</i>	)	Group Art Unit: 1614
	)	
Application Serial No.: 10/589,751	)	Examiner: Savitha M. RAO
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TETRAHYDROFOLIC ACID	)	

**DECLARATION UNDER 37 CFR.1.132**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, Virginia 22313-1450

Sir:

I, Fabrizio Marazza, declare as follows:

1. During the period prior to filing of Swiss Patent Application No. 00285/04 (having the priority date of February 20,2004), from which subject United States application was derived, I was the supervisor (R&D director) of both co-inventors of the subject application, i.e., Dr. G. Francese and M. Morosoli. Dr. G. Francese left the company few years ago. M. Morosoli is a technician still active at Cerbios-Pharma SA.
2. Several experiments were performed in order to find a suitable method of preparing (6S)-folinic acid. As stated in the US Application No. 10/589,751, several attempts to reproduce Example 6 of EP 0 293 751 (by Müller et al.), corresponding to U.S. Patent No. 6,160,116, always led to an untreatable, rubber like product.

3. A copy of the description of one of the experiments mentioned under point 2 is enclosed (a lab-journal page in Italian language). An English translation of this text is also enclosed.
4. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code.

F. Marazza

Fabrizio Marazza, PhD  
IP manager  
Cerbios-Pharma SA  
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Date

(6)-GF

Solubilità (6)-GF in H<sub>2</sub>O a 55°-60°CAPC vs 1.3  $\Rightarrow$  22063.4 units

Scalato 100 ml H<sub>2</sub>O a 55°-58°C Add (6)-GF C10834 a portione  
 ~ 4.2 g APC (dl 1:20)  $\Rightarrow$  C = 3.7%

Prova precipitazione Acido Folico derivante dalla sol di (6)-GF

1. (6)-GF (C10834) : 11.5 g (= 10g secchi)
2. H<sub>2</sub>O lenti : 300 ml
3. HCl 0.5 N

Scalato 1 in 2 a 58°C pH 7.5 Raffreddato a 10°C  $\rightarrow$  sol limpido  
 pH 8.33 Add HCl 0.5 N in 30' fino a pH 3.0 T = 9.7°C  
 (stato con HCl 0.5 N per 30' pH 2.10 a 10°C  
 FOT (p) e bialto 1 x 50 ml in 10'  $\rightarrow$  molto grigio  
 solido prima in Acetone  $\rightarrow$  gomma!

Analisi nel creatore vide 11.12

Am. Thiel

15.12.03

F. Marone

17.12.03



English translation of the lab-journal page no. 2246 (Notebook No. 23) / December 15, 2003  
by Moreno Morosoli

(The relevant description starts at line 5)

Test of direct precipitation of Folinic Acid from a solution of (6S)-CaF

1. (6S)-CaF (CJ0834): 11.5 g (= 10 g dry)
2. H<sub>2</sub>O (seralpure quality): 300 ml
3. HCl 0.5N

1. was dissolved in 2. at 58°C, pH 7.51. Solution was cooled to 10°C resulting in a clear solution., pH=8.23. During 30 min. under stirring 3. was added reaching a pH value of 3.0 (T=9.7°C). The mixture was stirred further during 30 min. adding 0.5 N HCl to keep the pH value at 3.0 and then the suspension was stirred for another hr (T=10°C). Filtration (D2) and washing with 50 ml of H<sub>2</sub>O gave an hygroscopic sticky solid. A tentative resuspension of this solid in acetone resulted in a rubberlike untreatable product.

"analysis" in folder No. 12

Translated by F.Marazza / July 29, 2010

*F. Marazza*